DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
M2658v1

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

March 17, 1999

WARNING LETTER
CHI-13-99

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Miles D. White
Chief Executive Officer
Abbott Laboratories
One Abbott Park Road
Abbott Park, IL 60064

Dear Mr. White:

During an inspection of Abbott Laboratories, Abbott Diagnostics Division (ADD), Abbott Park, Illinois, from September 8, 1998, to November 4, 1998, FDA determined that your firm continues to manufacture in vitro diagnostic products, which are medical devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above stated inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for, the manufacture, packing, labeling, storage, or installation are not in conformance with the Quality System Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Failure to establish and maintain procedures for implementing corrective and preventive action as required by 21 CFR 820.100. Your corrective and preventive action (CAPA) system failed to both trend and capture all incidents (in a timely manner) which may have reflected or indicated quality problems. This resulted in a failure to determine the course of adequate corrective and preventive action in several instances. For example:

   a. Corrective action for the TDx/TDx/FLx Flecainide assay was not implemented for more than ten months after Abbott first became aware of the issue, and preventive action for the TDx/TDx/FLx Flecainide assay (to discontinue marketing the product) failed to address the underlying quality issues.

b. Non-Conforming Material Reports (NCMR) for [redacted] lots of Auszyme with conjugate failures were not entered into the CAPA system. NCMRs for seven lots of Auszyme with test kit failures were not entered into the CAPA system until [redacted] months from the test failure date. NCMRs for four lots of AUSRIA II 125 with test kit failures were not entered into the CAPA system until [redacted] months from the test failure date.

c. A process validation failure for the AxSYM Total PSA conjugate occurred on 6-18-98. An NCMR was not written until [redacted] months later on 9-15-98, with entry into the CAPA system on 9-22-98.

d. The PSA IMx microparticle concentrate failed microbial specifications on 6-6-98. An NCMR was not written until more than [redacted] months later on 9-23-98, with entry into the CAPA system later in September.

e. Lots which fail (protein testing) at an early processing stage, such as viral lysate, are designated as "discontinued" and are not entered into the CAPA system for tracking and trending.

f. No hold time or age limitation was assigned to bulk Auszyme monoclonal conjugate although investigation of the failure of several master kit lots to meet release requirements revealed the necessity to limit the age of conjugate when combining kit components to form a master lot configuration.

g. SOP Op.A407 addressing the stability program does not include a provision to create a nonconforming material report for a stability failure. These failures are not adequately incorporated into the CAPA system for analysis.

2. Failure to document all activities required by 21 CFR 820.100(b) as they relate to corrective and preventive action. For example:

a. There is no documentation of the management review and approval of the decision not to send a customer communication to alert Axsym instrument users of a system software defect which causes incorrect test results to be reported.

b. The design verification test performed for the Abbott Commander [redacted] software version [redacted] identified unit test failures. Repeat testing did not include test failures or address failure to meet specifications. Management review of the [redacted] verification test indicated no problems were identified.

3. Failure to validate a process, the results of which cannot be fully verified by subsequent inspection and test, with a high degree of assurance as required by 21 CFR 820.75(a). For example:

   a. The validation protocol for PVA 98061850 Total PSA H50 conjugate concentration did not define acceptance criteria for conjugate potency.

   b. The protocol for PVA 980603002, Microparticle co-coating process validation of [redacted] Total PSA, required microbial membrane filtration samples to be collected. Protocol did not identify acceptance criteria for microbial samples and the summary report did not address the microbial test results.

   c. The precursor codes for PSA purification do not have defined specifications but are referred to as "For Manufacturing Use."

4. Failure to establish a quality plan which defines the quality practices, resources, and activities relevant to devices that are designed and manufactured, and to establish quality system procedures and instructions, including an outline of the structure of the documentation used in the quality system, as required by 21 CFR 820.20(d) and 820.20(e). For example:

   a. Numerous instances were found whereby documentation, instructions, and data which were utilized for quality assessments were not referenced in the quality plan. For example, not all procedures/systems associated with the corrective and preventive action system are identified. Your quality plan (Quality System Manual) fails to include a "Document Index," identify document hierarchy, and/or linkages between policies, procedures, work instructions, etc.

b. In your November 25, 1998 response to FDA 483 item #1, you stated that material disposition is electronically changed to on hold (OH) status via the Abbott Manufacturing Management (AMM) system in accordance with op.J325, Product Release/Approval. However, the diagram for corrective and preventive action did not include or refer to this procedure. The inspection also revealed additional examples whereby manual records failed to correlate with computer-generated documents involving the same issue, e.g., complaints and document titles.

5. The degree of control over the thawing process for certain in-process material ([redacted]) as required by 21 CFR 820.70 may not be adequate to assure conformance to the established maximum of three freeze-thaw cycles in that the number of times the material is thawed cannot be accurately determined from review of the manufacturing document or through the computerized materials management system.

This letter is not intended as an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the Form FDA 483 (enclosed) issued to Robert C. Doss, Vice President, Quality Assurance/Regulatory Affairs at the close of the inspection, may be symptomatic of serious underlying problems in your firm's quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be system problems, you must promptly initiate permanent corrective actions. Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket approval applications (PMA) or product license applications (PLA) for devices to which deviations from the Quality System Regulations are specifically related will be approved until violations have been corrected. Also, no requests for Export Certificates will be approved until the violations relating to your IVDs have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or administrative actions, such as civil penalties.

We acknowledge receipt of Dr. Doss's response to our Form FDA 483 dated November 25, 1998 (which was written following a meeting with Chicago District on November 12, 1998), and the revised consolidated inspection commitment schedule dated January 8, 1999 (which was presented during a meeting with FDA on January 8, 1999, at the Chicago District office). It is not possible to determine the complete adequacy of your responses/commitments until we are able to conduct an on-site facility inspection. During this next inspection, we will verify promised corrections, and otherwise determine the adequacy of your proposals as implemented at Abbott ADD.

Please notify this office in writing within 15 working days of receipt of this letter regarding any additional steps you have taken to correct these violations. Your response should be sent to Richard Harrison, Acting Director, Compliance Branch, U.S. Food and Drug Administration, 300 South Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

Sincerely,

/s/
Raymond V. Mlecko
District Director

Enclosure

cc: Ms. Marcia Thomas, Vice President
Corporate Quality Assurance/Regulatory Affairs
Abbott Laboratories
100 Abbott Park Road
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cc: Mr. Thomas D. Brown, President
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cc: Dr. Robert C. Doss, Ph.D.
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cc: Mr. Matthew Klamrzynski, Director
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